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Placement of a Fenestrated Palmaz Stent Across the Renal Arteries. Feasibility and Outcome in an Animal Study

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Objectives: *to investigate the feasibility of placing stents across renal arteries.*
Design: *we have studied in pigs: (i) the feasibility of accurately placing a fenestrated stent in front of one renal ostium; (ii) the short-term effects on renal arteries and function after the placement of such a fenestrated stent.*
Materials and methods: *eight fenestrated Palmaz stents were placed over pigs' renal ostia under fluoroscopy. Five weeks later, angiograms were performed and the animals were sacrificed. Proliferation of the healing tissues over the ostia was measured and analysed by microscopy. Serum creatinine was measured prior to all angiograms and at 5 weeks.*
Results: *all eight stents were correctly placed. One stent later migrated and was excluded from the study. One pig died at day 1. Gross examination confirmed the correct placement of the fenestrations in four pigs out of seven (57%). In the six remaining pigs, at 5 weeks, there was no angiographic evidence of stent misplacement and all the kidneys were fully perfused. Nine renal ostia were covered by struts and neointima with a mean area of coverage of 38 ± 5% altogether. No tissue proliferation was observed over the three renal ostia located in front of the fenestration. Serum creatinine did not significantly increase at 5 weeks.*
Conclusion: *creating a fenestration in a stent for renal arteries may be worth while in order to avoid neointimal covering of the renal ostia. However, accurate placement of such a fenestrated stent remains a difficult task.*

Key Words: Palmaz stent; Fenestration; Renal arteries.

Introduction

Endovascular stent-grafting of infrarenal aortic aneurysms requires a proximal neck long enough to allow fixation. A short neck makes accurate placement more difficult, or even impossible. If the stent is placed too low, overlying the aneurysm thrombus rather than the aortic wall, there is a risk of leakage or of stent migration. If it is placed too high, there is a risk that the renal circulation may be compromised.

The scope for endovascular stented graft might be broadened if the proximal fixation device could be placed intentionally at or above the renal arteries without jeopardising them. The stent design would have to be adapted to avoid coverage of renal ostia by the stent struts. We therefore modified a Palmaz stent by creating a fenestration in the device which, when correctly placed in front of one renal artery ostium, would not compromise the renal blood flow. We then set up a controlled study in pigs to assess the behaviour of these modified Palmaz stents when the lateral fenestration was placed in front of one renal artery ostium, the other ostium being covered by the non-modified part of the stent. This study was designed to test: (i) the feasibility of accurately placing a fenestrated Palmaz stent across the renal artery ostia in pigs, (ii) the effects of placing the fenestration and the non-modified part of the stent on the aorta and renal arteries, and renal function at 5 weeks.

Materials and Methods

Fenestrated Palmaz stents

The Palmaz balloon-expandable stents (P394, provided by Johnson & Johnson; 1, Central Parc, Avenue Sully Prudhomme, 92298 Chatenay Malabry, France) were 2.5 mm in diameter and 39 mm long unexpanded and

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up to 9 mm in diameter and 30.6 mm long once fully expanded. The Palmaz stents are slotted stainless-steel tubes with a diamond-shape design. To produce the fenestrated version (which was designed at the École de Biomécanique de Marseille, France) the stents were expanded to a diameter of 4 mm with a balloon and four consecutive struts were cut under a microscope in order to create a fenestration in the struts. The residuals were smoothed using laser abrasion. The stent was then mounted on a balloon, compressed to its initial 2.5-mm diameter, and sterilised using ethylene oxide. Three 3-mm-long titanium vascular clips (Ethnor, Neuilly, France) were used as radio-opaque markers. During the procedure, they were arranged as follows: one above the fenestration and two laterally in order to position the device correctly (Fig. 1.)

Procedures

Male pigs ($n=8$) weighing 30–32 kg were used. All procedures complied with the "Principles of Laboratory Animal Care" and "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 80-23 revised 1985). Serum creatinine levels were measured in all animals before any imaging was performed. The pigs were premedicated with Asaperone (Stressnyl®, 1 ml/10 kg) and anaesthesia was induced using sodium pentobarbital (20 mg/kg). The animals were mechanically ventilated with 2:1 mixture of air and oxygen. Cefamandol (1 g) was administered intravenously preoperatively and sodium heparin (100 IU/kg) before the stent deployment.

All the stenting procedures and angiograms were performed in an angiographic laboratory. After surgical preparation of the right groin, the femoral artery was exposed and a 10-F-diameter-long introducer with removable valve (Cordis, Issy les Moulineaux, France) was inserted. Angiograms were performed with a C-arm from four angles (front, lateral view, 30°, 60°) in order to assess the angle of origin of the renal arteries. The mean inter-renal aortic diameter was 7.8 mm as measured by a graduated pigtail catheter (Cook, Bjaeverskov, Denmark). The Palmaz stents were mounted on a balloon 4 cm in length and 8 or 9 mm in diameter (Boston Scientific SA, Saint Quentin en Yvelines, France). The stents were placed over the renal artery ostia with a 10% overdilatation under radiological control using a road-mapping technique. Different views were taken in an attempt to accurately place the stent. By rotating the balloon, the fenestration was placed in front of the renal artery that emerged closest to the frontal plane and the balloon was inflated under a pressure of 12 atmospheres. After deflation and withdrawal of the balloon, the stent position was checked with a further angiogram. When the procedure was completed, the femoral arteriotomy was closed and the animals were allowed to recover. Each step of the procedure was recorded on VHS videotape and the most significant images were printed. Anticoagulation was not used during the postoperative period.

Follow-up

Five weeks later, the animals were anaesthetised using the same technique. Blood samples were taken to measure serum-creatinine levels. New angiograms were obtained via a left femoral puncture to locate the position of the stent and to determine the patency of the renal arteries and aorta. Images were again recorded on VHS videotape and printed. Two observers independently reviewed the angiograms. Renal artery stenosis was defined as any reduction of the area of the renal ostia. Before sacrificing the animals, the aorta was clamped above the renal arteries. The aorta was then catheterised and infused with normal saline. After clamping below the renal arteries and the renal arteries themselves, the whole block of tissue was pressure-fixed with 10% buffered formaldehyde. Two samples were fixed in Trump (6.75 mM NaOH, 10 mM NaH_2PO_4, 4% formaldehyde, and 1% glutaraldehyde) for examination under scanning electron microscopy (SEM). The abdominal aorta (containing the stent), the renal arteries and the kidneys were then resected "*en bloc*". In order to evaluate the stenosis immediately after a stent placement, a non-modified Palmaz stent was deployed at the 5-week follow-up in three pigs across the mesenteric artery, then fixed in a pressure-distended state and the animals were sacrificed immediately.

Macroscopic examinations

The aortas ($n=8$) were opened longitudinally and photographs of the specimens were taken. Gross macroscopic examination was performed to detect areas of renal infarction, aortic or renal arterial thrombosis and stent expansion.

Tissue proliferation over the ostia was assessed using binocular lenses and was measured using a micrometric scale. For each ostium, the percentage of ostial cross-section covered by metal struts was

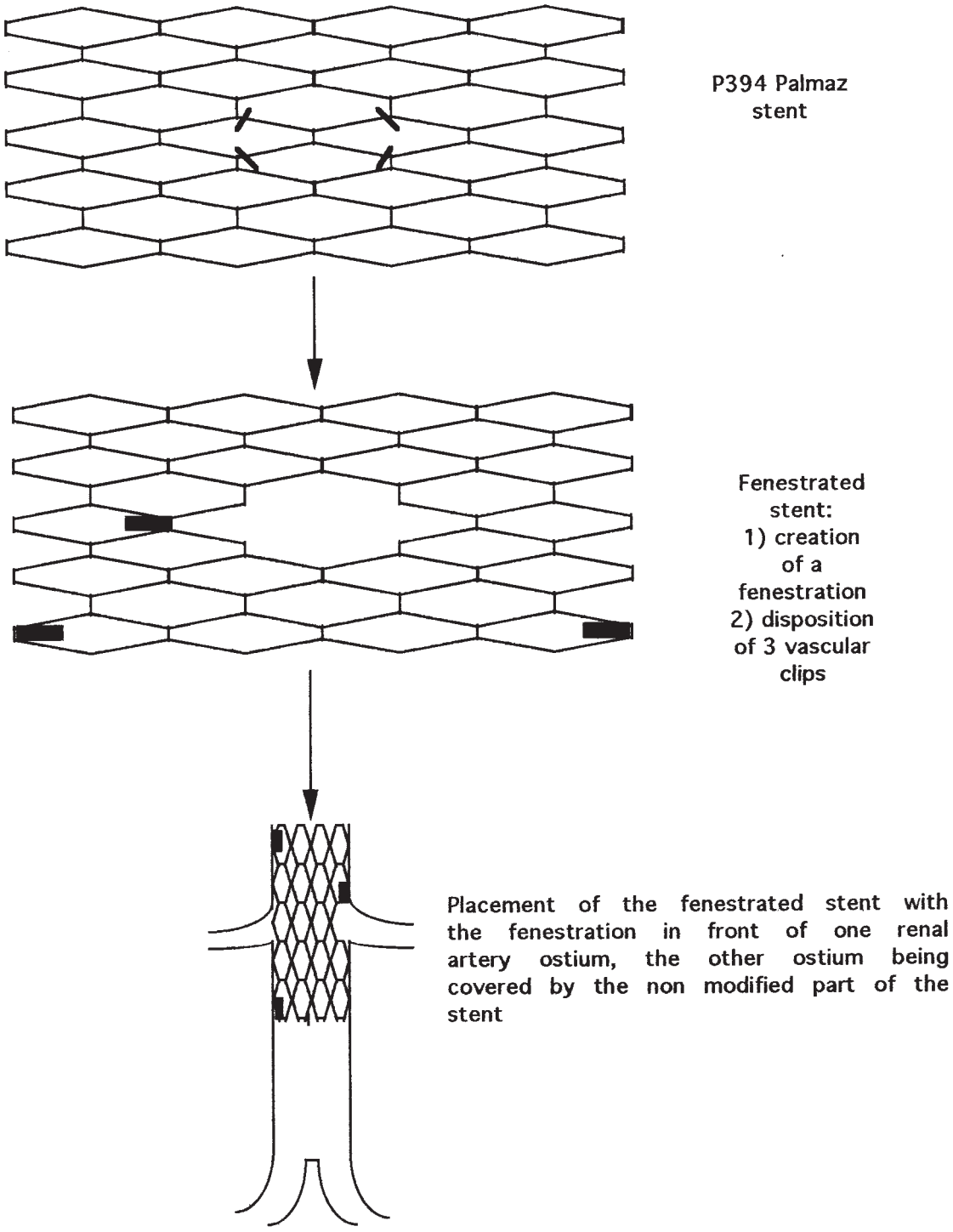

Fig. 1. Creation and placement of the fenestrated P394 Palmaz stent.

measured as well as the area of the struts covered by healing tissues and the area of the interstices covered by healing tissues overhanging the edges of the struts. Results were expressed as a ratio of the area of stent struts and healing tissues covering the renal ostium divided by the total area of the renal artery ostium.

Histology

After fixation, the samples were dehydrated with ethanol solutions of increasing concentrations and then embedded in paraffin. After removal of the struts, 10-µm cross-sections were obtained and stained using

Meyer's haematoxylin–eosin or tested for expression for factor VIII (antibodies purchased from DAKO, Trappes, France).

Results

Procedure

In one pig, the stent was displaced downstream below the renal arteries during balloon withdrawal. A new balloon was inserted which allowed accurate replacement of the stent over the renal artery ostia. All eight stents were correctly placed over the renal artery ostia at the end of the first procedure.

Angiographic assessment at 5-week follow-up

Seven pigs weighing 37–39 kg survived the 5-week follow-up period without any sign of peripheral vascular insufficiency. One animal died at day 1 due to massive haemorrhage at the groin and was included in the feasibility study but excluded for the angiographic and pathological studies.

At 5 weeks, angiograms were obtained for seven animals. The mean inter-renal aortic diameter was 7.9 mm (NS = not significant). However, in one pig the stent had migrated to 2 cm below the renal arteries. This was due to a size discrepancy between the stent and the aorta and this animal was excluded from the study.

In the six remaining animals, there was no angiographic evidence of stent misplacement. No secondary migration or distortion of the stents occurred and no aortic or renal thrombus was observed. The renal arteries appeared to be normal in all six pigs on the angiogram (Fig. 2). The kidneys were symmetrically and fully perfused in all animals.

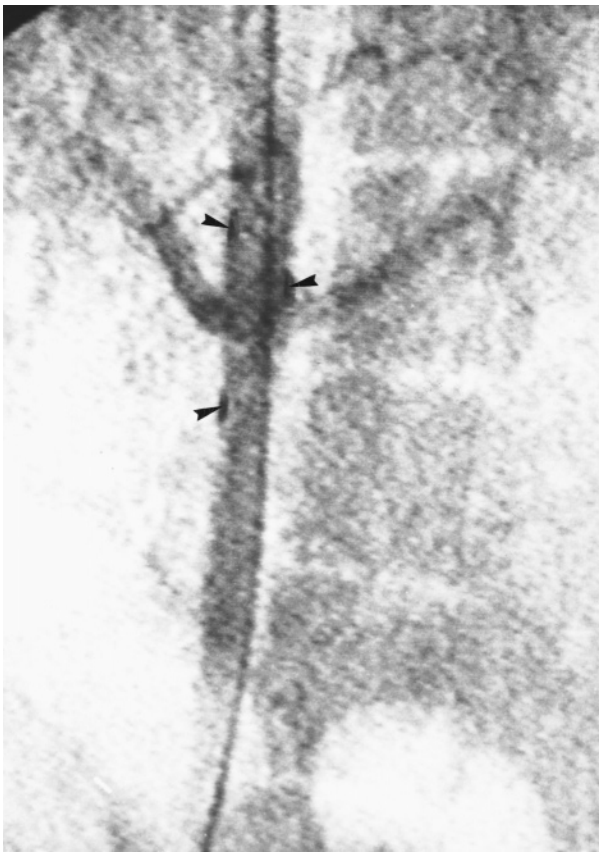

Fig. 2. Five-week angiogram showing the fenestrated Palmaz-stent placement. The fenestration is correctly placed in front of the left renal artery ostium. Renal arteries are patent without stenosis. (Arrows: vascular clips.)

Feasibility of placing the fenestrated Palmaz stent

In the seven samples available for the feasibility study, gross examination confirmed correct placement of the fenestration in front of the ostia in four pigs out of seven (57%) (Fig. 3). In the animal that died at day 1, the fenestration was correctly placed in front of one ostium and the other ostium was placed opposite the non-modified part of the stent. In the four successful cases, the origin of the renal arteries was in the frontal plane. In the three unsuccessful cases, the fenestrations were on the same horizontal plane as the ostia but were misplaced (Fig. 4). In those cases, the angle of the origin of the renal arteries varied and was not in the frontal plane.

Macroscopic evaluation

In the six samples available for the pathological study, three ostia were located in front of the fenestration and nine ostia were covered by the non-modified part of the stent. Among them, the percentage of ostial cross-sections covered by metal struts was assessed to be $13 \pm 2\%$. This was confirmed by the non-modified Palmaz stents deployed across the mesenteric artery. The luminal surface of the stents was glossy and the stent struts over the aortic wall were covered uniformly with a thin film of healing tissue. At the renal artery ostia, the healing tissue had entirely covered the renal sides of the struts whereas the aortic sides were only partially covered. The healing tissue extended over the spaces between the struts with a mean area coverage of

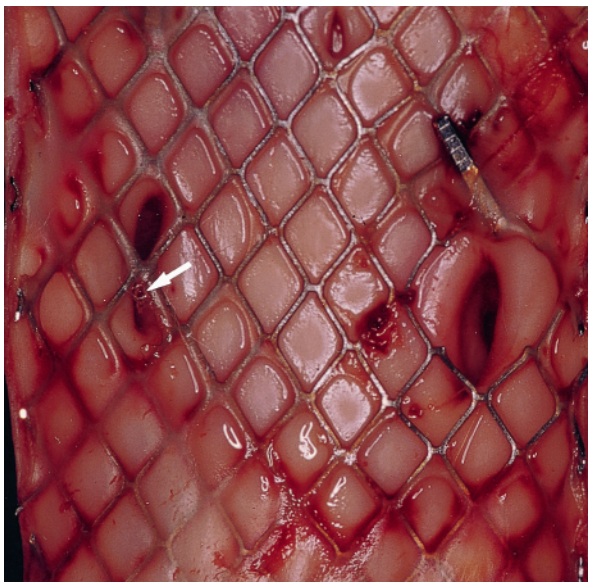

Fig. 3. The fenestrated Palmaz stent is correctly placed with the fenestration in front of the left renal ostium, the other being covered by the stent struts. Neointima is not seen in front of the left ostium. Neointima is seen in front of the right ostium extending from the stent struts (arrow).

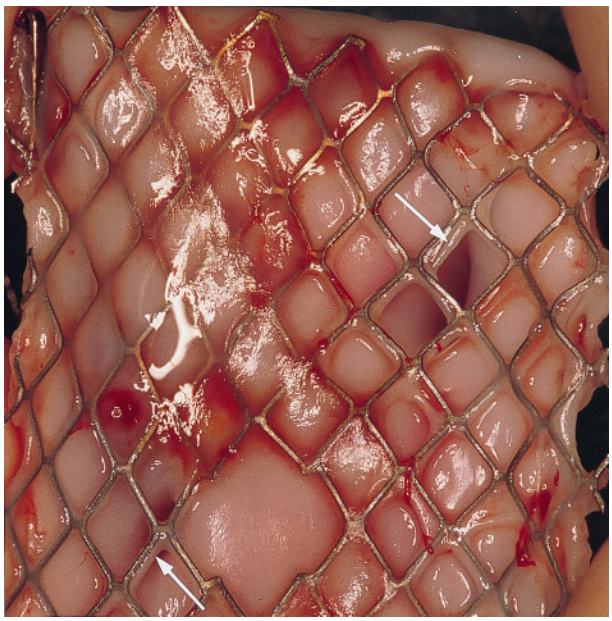

Fig. 4. The fenestrated Palmaz stent is incorrectly placed. The struts and neointima extending from stent struts cover both ostia (arrows).

$25 \pm 5\%$ (range 5–39%). Finally, the mean area covered by the struts and healing tissue was $38 \pm 5\%$ of renal artery ostia. Simultaneously, no healing tissue was seen over the three renal ostial struts located in front of the fenestration. The wall of the renal artery trunk remained normal in all samples.

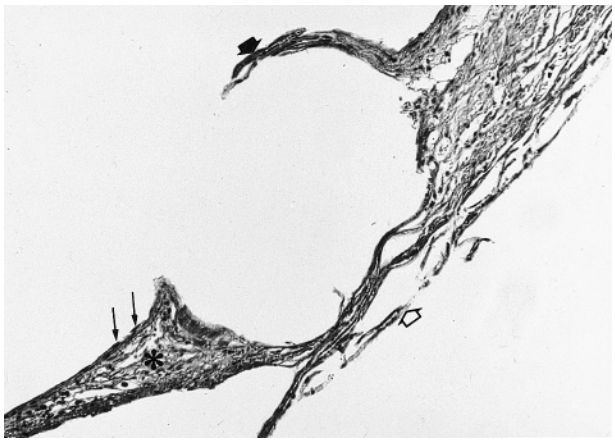

Fig. 5. Histological findings after removal of stent struts crossing the level of a renal artery ostium. The neointima entirely encircles the renal side of the strut (white arrow) and partially covers the aortic side (black arrow) and is progressing towards the lumen, creating a free-floating edge (*). The neointima was made up of myofibroblastic elements covered with endothelial cells (double arrows). (Original magnification $\times 500$.)

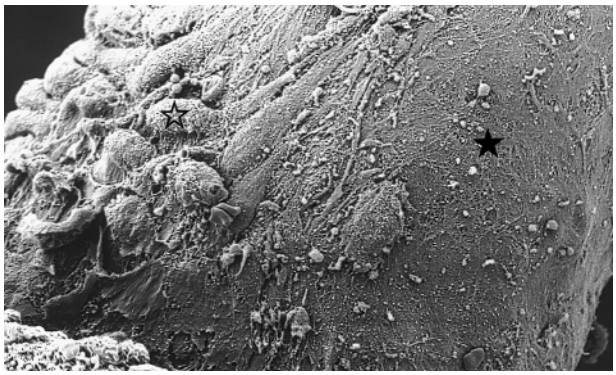

Fig. 6. Scanning electron microscopy of a stent strut covering a renal artery ostium. (★): Aortic side of the stent strut not covered with neointima. (☆): Renal side of the stent strut covered with neointima and endothelial cells. (Original magnification $\times 1100$.)

Histology

The stents were lying against internal elastic lamina of the aortic wall without evidence of penetration. No "foreign body" cellular reaction was seen around the struts. Over the aortic wall, in the area surrounding the renal ostia, a thickened neointima covered the stent struts. At the level of renal artery ostia, the neointima had entirely encircled the renal side of the struts, partially encircled the aortic side and progressed towards the lumen, creating a free-floating edge (Fig. 5). The neointima was composed of myofibroblastic elements covered with endothelial cells as assessed by positivity for factor VIII and SEM morphology (Fig. 6).

Renal assessment

The kidneys were submitted to a macroscopic and microscopic evaluation. There was no infarction. Serum creatinine increased from 71.1 ± 7.1 μmol/l before stent implantation to 82 ± 7.2 μmol/l at 5 weeks (NS).

Discussion

Endovascular repair of an abdominal aortic aneurysm (AAA) requires fixation of an endovascular stent-graft in a segment of normal infrarenal aorta. The applications for these devices could be broadened if the proximal stent could be positioned at or above the renal artery ostia. We have therefore modified a Palmaz stent by creating a fenestration in the struts, which, if correctly positioned in front of one renal artery ostium, would not compromise the renal blood flow.

Accurate placement of the fenestrated stent seems a straightforward procedure, but gross examination confirmed correct placement of the fenestration in front of the ostia in only four pigs out of seven (57%). In the four successful cases, the origin of the renal arteries was in the frontal plane. Unsuccessful placements can mostly be explained by the origin of renal arteries at an oblique angle from the aorta. Fluoroscopic guidance provided only uniplanar view, thus limiting the accuracy of deployment of the modified stent in front of renal arteries that did not emerge in the frontal plane. Nevertheless, when the fenestration was correctly placed in front of the ostium, no neointimal tissue developed. Dimensional information delivered by angiography was also of limited value, due to inaccuracies produced by image magnification and parallax errors. In clinical practice, the study of the origin and angulations of renal arteries is best evaluated by a spiral computed tomography (CT) scan.[1] Intravascular ultrasound could be an extremely useful adjunct to angiography when used to determine the morphology of vascular structures and to perform real-time observation of the accurate deployment of the stent in front of the renal artery ostia. Bilateral fenestration would be theoretically possible. To our knowledge, there are no literature data concerning how a fenestration affects radial force, hoop strength and stent fixation.

This study also assessed the effect of the intentional or accidental placement of a non-modified Palmaz stent in front of renal arteries. The stent struts themselves covered 13% of ostial cross-section. In addition, neointima overhanging the edges of the struts continued between the struts and created a mean narrowing of 38%. In the present study, the degree of stenosis was estimated with precision because the aorta and renal arteries were removed in a pressure-distended state and fixed at their *in vivo* size. Angiograms showed that the renal blood flow was not jeopardised and renal function had not deteriorated at 5 weeks' follow-up. The slight increase in creatinine reflects increasing musculature of the growing pigs. The development of neointima between the struts suggests that there is some hazard associated with the long-term placement of an endovascular stent across renal artery ostia. Dawson *et al*.[2] reported that six out of 27 (22%) renal arteries covered with Palmaz stents in a canine model were narrowed after 30 weeks' mean follow-up and that, in two of them, the narrowing was severe and diffuse and associated with histological evidence of ischaemic renal parenchyma injury.

The shape and composition of the different stent struts may also influence neointima formation. Strecker stents knitted from tantalum with interlocking loops deployed in the aorta of pigs caused stenosis or occlusion in seven out of 18 (39%) renal arteries[3] with an excessive neointima proliferation over a surface of 43 ± 30% (range 0–84%). Memotherm® stents made of Nitinol with roughened laser-etched surface caused ostial occlusion in almost all cases.[4] The better results of Palmaz stents might be related to a lower metal-to-ostial area ratio. The Wallstent®, which has smooth rounded struts of knitted sprung-steel wires, has no deleterious effect on renal patency or renal function at 6 weeks' follow-up.[4,5]

Clinical experience in humans suggests that stents placed across the ostia of branch vessels do not compromise renal blood flow. In Parodi's series of stented graft for AAA, six patients out of 50 had their renal artery ostia accidentally covered by the Palmaz stent which supported the endovascular graft.[6] He reported neither lost kidneys nor impairment of renal function. Wain *et al*.[7] and Marin *et al*.[8] with a graft constructed from a large Palmaz stent and an expanded polytetrafluoroethylene (ePTFE) graft obtained similar results. In this last series, the bare portion of the stent was appropriately placed across the renals in 35 patients without any occlusion or renal dysfunction. This technical option also significantly reduced the risk of proximal endoleak compared to an endograft implanted below the renal arteries. However, two patients had accidental coverage of one renal ostium leading to non-dialysis-dependent renal insufficiency. The Leicester group prefer the deployment of the Palmaz stent below the renal arteries.[9] The uncovered

part of the Perth bifurcated system,[10] in which proximal fixation is provided by a Gianturco Z-stent, was deployed intentionally across the renal arteries ostia in 18 out of 21 patients (86%). There was no associated renal artery occlusion or deterioration in renal function at a 30 weeks' mean follow-up (range 4–60). Similarly, in Malina's study[11] in which a Gianturco Z-stent covered 25 renal arteries in 18 patients treated for AAA, no impairment of renal function was observed after 6 months and there was only one case of partial lower-pole infarction. According to these small non-randomised studies, deployment of such "wide mesh" stents across the renals in humans appears to be safe in the short term. However, animal studies need to make us cautious in the long-term. Mirich *et al.*[12] found diffuse cortical atrophy in animals at 7 months' follow-up when neointima built up around the porous nylon mesh which was used to cover a Gianturco stent graft, even though angiographically the renal arteries looked normal. In the French Vanguard multicentric study with a mean follow-up of 18 months, the bare Nitinol part of the stent graft was placed across the ostia of the renal arteries in five patients out of 75 (7%). In one patient, one of the renal arteries thrombosed without any clinical consequences. Another patient experienced renal failure (400 μm/l creatinine) and hypertension.[13] Irrespective of the risk of early thrombosis, there remains the long-term risk of red-cell fragmentation and microembolisation from platelet aggregates.

In summary, this study suggests that in animals the placement of conventional Palmaz stents over the renal arteries may reduce the cross-sectional area of the renal artery lumen and compromise renal blood flow.

Creating a fenestration in a stent for renal arteries may be worth while in order to avoid neointimal covering of the renal ostia. However, accurate placement of such fenestrated stent remains difficult. Further investigations need to be pursued in order to optimise the placement of such stents.

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